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RESEARCH ARTICLE

Association between ambient air pollution exposure and infants small for gestational age in Huangshi, China: a cross-sectional study

Jiayuan Hao[1] · Faxue Zhang[1] · Dieyi Chen[1] · Yanyun Liu[2] · Lina Liao[2] · Cui Shen[2] · Tianyu Liu[1] · Jingling Liao[3] · Lu Ma[1,4]

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Abstract

Small for gestational age (SGA) is defined as intrauterine growth retardation or small sample, referring to the 10th percentile of birth weight lower or two standard deviations less than the average weight at the same gestational age. SGA infants bring great economic and psychological burdens to families and society. The association between exposure to air pollution and SGA in underdeveloped cities with poor air quality remains unclear. Thus, this study is conducted to estimate the effects of maternal exposure to air pollutants on SGA numbers. Birth information was collected from the Huangshi Maternity and Children's Health Hospital from January 1st to December 31st in 2017. Data of pregnancy exposure were accessed using stationary monitors. These data included particulate matter less than or equal to 10 μm in aerodynamic diameter (PM_{10}), particulate matter less than or equal to 2.5 μm in aerodynamic diameter ($PM_{2.5}$), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2). Multivariate logistic regression models were performed to estimate the association between ambient air pollution and the risk of SGA during different exposure windows. It was found that a 1 $\mu g/m^3$ increase in air pollution concentrations during the entire pregnancy was associated with a higher risk of SGA, with an adjusted odds ratio (OR) and 95% confidence interval (CI) of 1.055 (1.035–1.076), 1.084 (1.053–1.116), 1.000 (0.953–1.049), and 1.051 (0.968–1.141) for PM_{10}, $PM_{2.5}$, NO_2, and SO_2, respectively. Thus, it is suggested that exposure to air pollution is associated with an increased risk of SGA. The effects of PM_{10} and $PM_{2.5}$ were more stable than NO_2 and SO_2.

Keywords Air pollution · Particulate matter · Nitrogen dioxide · Sulfur dioxide · Small for gestational age · Adverse pregnancy outcome

Introduction

Small for gestational age (SGA) is defined as intrauterine growth retardation or small sample, and it refers to the 10th percentile of birth weight lower or two standard deviations less than the average weight at the same gestational age (Ding et al. 2013; Khambalia et al. 2017; Lefebvre and Samoilenko 2017). Similarly, appropriate size for gestational age (AGA) is known as a birth weight within the 10th to 90th percentile of the reference value. SGA is associated with a higher risk of infant morbidity and mortality (Basso et al. 2006). In addition, it can lead to complications in later childhood, such as endocrine and metabolic disturbances (Clayton et al. 2007). However, the risk factors for SGA have not been fully identified, although there are some possible causes, such as teenage motherhood, previous preterm birth, and inadequate prenatal visits (Kildea et al. 2017).

Previous studies have illustrated that exposure to high concentrations of air pollution during pregnancy may decrease uterine blood flow and ultimately slow fetal growth (Browne et al. 2015; Kannan et al. 2006). Maternal exposure to air pollution during pregnancy may be one of the complex set of causes, which increases the risk of impaired fetal

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✉ Lu Ma
malu@whu.edu.cn

[1] Department of Healthcare Management, School of Health Sciences, Wuhan University, Wuhan 430071, China

[2] Huangshi Maternity and Children's Health Hospital of Edong Healthcare Group, Huangshi, Hubei Province, China

[3] Department of Public Health, Wuhan University of Science and Technology School of Medicine, Wuhan, China

[4] Global Health Institute, Wuhan University, Wuhan 430071, China

development and adverse birth outcomes, such as preterm birth and low birth weight (Lamichhane et al. 2015; Li et al. 2017). Whether there is potential association between air pollution and gestational age as a typical factor for fetal growth needs to be addressed.

China has been troubled with air pollution for many years, and the evidence remains inconsistent whether high levels of air pollutants affect the incidence of SGA. Although there are some analyses that have explored the association between air pollution and SGA, most of them have been conducted in developed countries or regions with relatively low air pollution (Michikawa et al. 2017; Rich et al. 2009b; Schlesinger et al. 2006; Wang et al. 2019). To our knowledge, there are no existing studies that have investigated the relationship between air pollution and SGA in central China. Huangshi is an industrial city in central China, and its economic growth has been attributed to mining and metallurgy in recent years (Zhan et al. 2017). Although the concentrations of air pollutants in Huangshi are lower than those in other industrial cities, such as Wuhan (Qian et al. 2016), air pollution exposure in Huangshi is still relatively higher than the air quality guidelines (AQG) issued by the World Health Organization (WHO 2005). For example, compared with the AQG guidelines, the 24-h mean concentrations of particulate matter less than or equal to 10 μm in aerodynamic diameter (PM_{10}) and particulate matter less than or equal to 2.5 μm in aerodynamic diameter ($PM_{2.5}$) exceeded the WHO standard for 327 days and 295 days, respectively, in 2017. There are many prefecture-level industrial cities in central China with low residential mobility, like Huangshi. However, due to subaverage economic and demographic factors, prefecture cities have often been ignored in previous studies. As pregnant women do not have access to advanced medical services during pregnancy as in developed areas, it has been suggested that there might be more severe birth outcomes when pregnant mothers are exposed to eternal environmental pollution.

We chose Huangshi as the study area to investigate whether there are associations between SGA and exposure to air pollution, including PM_{10}, $PM_{2.5}$, nitrogen dioxide (NO_2), and sulfur dioxide (SO_2). Logistic regression models were constructed in different quartiles to estimate the potential threshold effects. Previous studies have reported that different fetal sexes had different responses towards the environmental simulation in vivo and in vitro, suggesting that infant sex is related to the regulation of birth health (Al-Qaraghouli and Fang 2017; Catalano et al. 2014; Challis et al. 2013; Liu et al. 2018). We also conducted analysis among male infants and female infants during different exposure windows to compare the variation between the different sexes.

Methods

Study area

Huangshi (114°31′-115°30′ East, 29°30′-30°15′ North) is a prefecture-level city in the Hubei province of central China. The city covers an area of 4583 km^2 with a population of 2,689,300 people in 2017. With a subtropical monsoon climate, the city's weather is mild and humid. However, as an industrial city, Huangshi has high level of air pollutants according to the WHO guideline values (WHO 2005).

Study population

Information of mothers and their live births were collected from the Huangshi Maternity and Children's Health Hospital from January 1, 2017, to December 31, 2017. The annual number of births in this hospital accounted for more than 33% of the city's total delivery. The inclusion criteria included live singleton births after 24 completed weeks and within 42 weeks with complete covariates. In addition, infants whose birth weights were more than the 90th percentile of newborns needed to be excluded. Finally, 4194 singletons were identified (Fig. 1).

The covariates were collected from medical records documented by doctors and nurses after deliveries. The original data was recorded in medical report books and then transformed into electronic form. The collected variables included maternal age, parity, gestational age at birth, date of delivery, delivery mode, infant birth weight, infant sex, and maternal medical conditions during pregnancy including gestational hypertension and gestational diabetes mellitus. The date of conception was calculated using gestational weeks and the date of birth. The gestational age of infants in this study was defined using the adjusted last menstrual period and the delivery date. SGA was determined using a comparison of the weight ranges from the birth weight curve for China (Zhu et al. 2015).

Exposure assessment

Air pollutant concentrations were obtained from the mirror website of the Environmental Protection Agency (https://www.aqistudy.cn/historydata/). The 24-h daily concentrations of PM_{10}, $PM_{2.5}$, NO_2, and SO_2 were collected. The time-varying average concentration approach was utilized to estimate individual exposure.

According to the different exposure windows, a pregnancy period was divided into the first trimester (1–12 weeks), the second trimester (13–27 weeks), and the third trimester (28 weeks to delivery) (Wu et al. 2009).

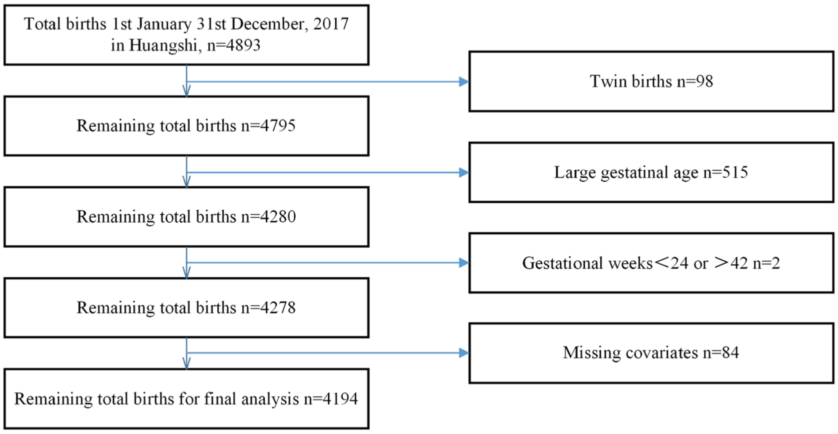

Fig. 1 Flow chart of the study population selection

Statistical analysis

The correlations between each air pollutant were calculated using the Pearson correlation. The chi-squared test for categorical variables and the independent sample *t* test for continuous variables were conducted for the univariate factor analysis of maternal and infant characteristics. A single-pollutant model and the calculated risk of SGA were conducted separately for each pollutant and pregnancy period.

To further explore the associations between air pollution and SGA, second-stage analyses were performed. Multiple logistic regression models adjusted for covariates were conducted to estimate the specified trimester association between air pollutants and SGA during the entire pregnancy, the first trimester, the second trimester, and the third trimester. All concentrations of pollutants were regarded as continuous variables, and the associations were shown as ORs and 95% CIs per 1 $\mu g/m^3$ increase in PM_{10}, $PM_{2.5}$, NO_2, and SO_2.

Stratified analysis of the associations in subgroups for female and male infants was estimated during the different periods. To further explore the effect of air pollutants for their per interquartile range (IQR) increase and to observe the possible threshold effect, the association within subgroups of different quartiles compared with the reference group of the first quartile was assessed. Due to periodic variations in air pollutants, the effects of these seasonal variations on the association of air pollution and SGA were estimated.

Additionally, multi-pollutant models were conducted to explore the potential confounding effects of other pollutants on SGA during each pregnancy period. Due to the high correlation of PM_{10} and $PM_{2.5}$, they were not included in one regression.

Statistical tests were two-sided, and a P value < 0.05 was considered statistically significant. All analyses were conducted using R 3.4.4 software with “tidyverse,” “rlist,” and “ggplot2” packages.

Results

The demographic characteristics of the mother–infant pairs are shown in Table 1. A total of 4194 deliveries that met the criteria were collected from the Huangshi Maternity and Children’s Health Hospital in 2017. A total of 315 (7.5%) of these deliveries were SGA infants, and 3879 (92.5%) were AGA infants. The mean gestational age was 38.69 for SGA infants and 38.42 for AGA infants. A total of 84.2% of the mothers were less than 35 years old at the time of delivery, 2.1% were diagnosed with gestational hypertension, 3.7% were accompanied with gestational diabetes mellitus, and for 46.2% of them, this was their first delivery. Gestational age, maternal age, parity, and gestational diabetes mellitus were not statistically significantly associated with the risk of SGA. The SGA percentile was higher in infants whose mothers were diagnosed with gestational hypertension. In addition, a significantly higher proportion of SGA infants among female newborns were observed ($P < 0.001$).

The average maternal exposures to the four air pollutants during the entire pregnancy are shown in Fig. 2. Women who delivered in summer had a higher exposure level to all the pollutants. The mean concentrations of PM_{10}, $PM_{2.5}$, NO_2, and SO_2 were 86.8 $\mu g/m^3$, 55.3 $\mu g/m^3$, 36.5 $\mu g/m^3$, and 17.6 $\mu g/m^3$, respectively. Compared with the AQG released by WHO (annual mean is 20 $\mu g/m^3$ for PM_{10}, 10 $\mu g/m^3$ for $PM_{2.5}$, and 40 $\mu g/m^3$ for NO_2; 24-h mean is 20 $\mu g/m^3$ for SO_2), the maternal exposure concentrations of PM_{10} and $PM_{2.5}$ were far above those criteria. The correlations of each of two pollutants were calculated and are shown in Table S1. PM_{10} and $PM_{2.5}$ were significantly associated with SO_2, and Pearson’s correlation coefficients were 0.804 and 0.788, respectively. NO_2 was less strongly correlated with the solid pollutants, and Pearson’s correlation coefficients for PM_{10} and $PM_{2.5}$ were 0.660 and 0.644, respectively.

Table 1 Summary characteristics of participants

Characteristics	SGA, *n* = 315	AGA, *n* = 3879	*t*/chi-square (*P*)
Gestational age (weeks, mean (SD))	38.69 ± 2.01	38.42 ± 1.91	0.403
Maternal age, *n* (%)			
≤ 24	74 (23.5)	812 (20.9)	0.598
25–29	104 (33.0)	1404 (36.2)	
30–34	84 (26.7)	1054 (37.2)	
≥ 35	53 (16.8)	609 (15.7)	
Parity, *n* (%)			
0	158 (50.2)	1780 (45.9)	0.144
≥ 1	157 (49.8)	2099 (54.1)	
Gestational hypertension, *n* (%)			
Yes	15 (4.8)	74 (1.9)	0.001
No	300 (95.2)	3805 (98.1)	
Gestational diabetes mellitus, *n* (%)			
Yes	9 (2.9)	147 (3.8)	0.400
No	306 (97.1)	3732 (96.2)	
Delivery mode, *n* (%)			
Vaginal	157 (49.8)	1874 (48.3)	0.601
Cesarean	158 (50.2)	2005 (51.7)	
Infant sex, *n* (%)			
Male	114 (36.2)	2243 (57.8)	< 0.001
Female	201 (63.8)	1636 (42.2)	

Chi-square test for categorical variables and independent sample *t* test for continuous variables

The crude ORs and adjusted ORs (adjusted for maternal age, parity, gestational hypertension, gestational diabetes mellitus, delivery mode, and infant sex) with 95% CI for each air pollutant and pregnancy period are presented in Table 2. The variation between crude ORs and adjusted ORs was subtle. Exposure to PM_{10} and $PM_{2.5}$ was significantly associated with a risk of SGA during the entire pregnancy (aOR [95% CI], 1.055 [1.035–1.076] for PM_{10} and 1.084 [1.053–1.116] for $PM_{2.5}$), and the adverse effects of $PM_{2.5}$ were stronger than those of PM_{10}. The effects of NO_2 and SO_2 were statistically significant during the first and third trimesters. For all of the pollutants, the highest ORs occurred during the third trimester (aOR [95% CI], 1.018 [1.012–1.024], 1.022 [1.013–1.030], 1.037 [1.019–1.056], and 1.117 [1.082–1.153] for PM_{10}, $PM_{2.5}$, NO_2, and SO_2, respectively). The lowest ORs appeared during the first trimester, showing as an inverse effect on SGA (aOR [95% CI], 0.979 [0.971–0.987], 0.976 [0.966–0.986], 0.959 [0.945–0.973], 0.887 [0.857–0.919], respectively). The

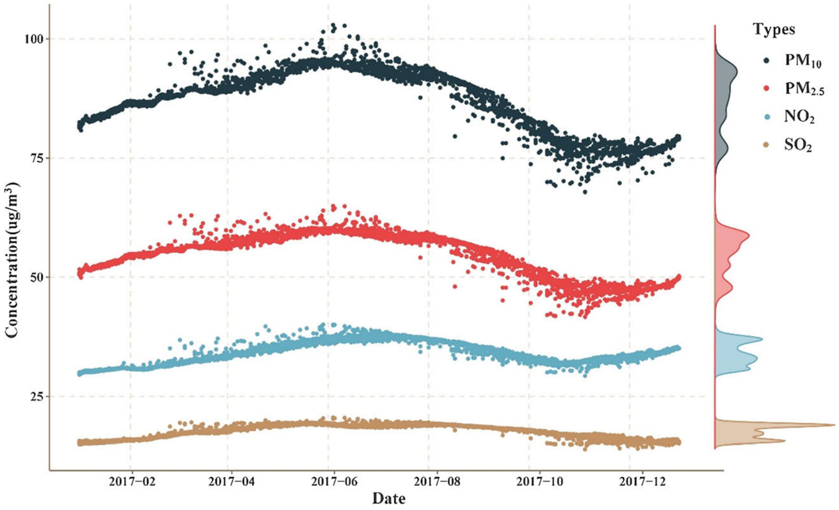

Fig. 2 Mean concentrations of maternal exposure to four air pollutants including PM_{10}, $PM_{2.5}$, NO_2, and SO_2 during entire pregnancy

Table 2 Crude and adjusted ORs (95% CIs) for SGA associated with every 1 μg/m^3 increase in air pollutants

Exposure	Crude			Adjusted		
	OR[a]	95% CI	*P*	*a*OR[b]	95% CI	*P*
PM_{10}						
Entire pregnancy	1.692	1.384–2.042	< 0.001	1.055	1.035–1.076	< 0.001
Trimester 1	0.817	0.753–0.886	< 0.001	0.979	0.971–0.987	< 0.001
Trimester 2	1.138	1.062–1.219	< 0.001	1.013	1.006–1.020	< 0.001
Trimester 3	1.184	1.116–1.255	< 0.001	1.018	1.012–1.024	< 0.001
$PM_{2.5}$						
Entire pregnancy	2.179	1.644–2.917	< 0.001	1.084	1.053–1.116	< 0.001
Trimester 1	0.792	0.722–0.877	< 0.001	0.976	0.966–0.986	< 0.001
Trimester 2	1.207	1.094–1.318	< 0.001	1.019	1.009–1.028	< 0.001
Trimester 3	1.219	1.127–1.331	< 0.001	1.022	1.013–1.030	< 0.001
NO_2						
Entire pregnancy	1.020	0.638–1.629	0.947	1.000	0.953–1.049	0.913
Trimester 1	0.665	0.580–0.776	< 0.001	0.959	0.945–0.973	< 0.001
Trimester 2	1.184	0.990–1.411	0.065	1.016	0.998–1.035	0.079
Trimester 3	1.424	1.195–1.692	< 0.001	1.037	1.019–1.056	< 0.001
SO_2						
Entire pregnancy	1.629	0.722–3.707	0.238	1.051	0.968–1.141	0.253
Trimester 1	0.319	0.224–0.449	< 0.001	0.887	0.857–0.919	< 0.001
Trimester 2	1.357	0.951–1.913	0.091	1.029	0.993–1.066	0.120
Trimester 3	2.814	2.061–3.873	< 0.001	1.117	1.082–1.153	< 0.001

[a] Crude ORs of air pollutants

[b] Adjusted ORs for covariates, including maternal age, parity, gestational hypertension, gestational diabetes mellitus, delivery mode, and infant sex

effects of air pollutants per IQR increase are presented in Table 3, with the first quartile as a reference. In the case of PM_{10} and $PM_{2.5}$, the risk of SGA through the entire pregnancy increased; however, there were no observable remarkable variations among the different quartiles. The effects of PM_{10} and $PM_{2.5}$ were obviously strengthened for per IQR rise in pollutants during all the different trimesters. NO_2 showed a positive gradient increase in the risk of SGA, with quartiles of exposure in the third trimester ranging from 1.587 to 2.375. Referring to the first quartile, the effects of SO_2 increased with the successive quartiles 2, 3, and 4 during the first and third trimesters.

In the stratified analyses by sex, the effects of air pollution exposure were stronger on male infants (Fig. 3). Exposure to PM_{10} and $PM_{2.5}$ was statistically significant during each pregnancy period as pooled infants. The ORs with 95% CIs of PM_{10} were 1.067 (95% CI 1.033–1.103) for males and 1.049 (95% CI 1.024–1.076) for females during the entire pregnancy. The ORs with 95% CIs of $PM_{2.5}$ were 1.100 (95% CI 1.049–1.154) for males and 1.077 (95% CI 1.038–1.117) for females during the entire pregnancy. The effects of NO_2 and SO_2 for the two sexes were still statistically significant during the first and third trimesters. The variation between male and female infants during the third trimester was small, and the ORs with 95% CIs of male and female infants were 1.019 (95% CI 1.009–1.029) and 1.018 (95% CI 1.010–1.026) for PM_{10}, 1.020 (95% CI 1.007–1.034) and 1.022 (95% CI 1.012–1.033) for $PM_{2.5}$, 1.043 (95% CI 1.013–1.074) and 1.034 (95% CI 1.011–1.057) for NO_2, and 1.116 (95% CI 1.061–1.174) and 1.119 (95% CI 1.009–1.029) for SO_2.

Two pollutant models were developed to examine the potential confounding effects of other pollutants in our model (Fig. 4). Compared with a single-pollutant model for PM_{10} and $PM_{2.5}$ (1.055 1.035–1.076 for PM_{10} and 1.084 1.053–1.116 for $PM_{2.5}$), the effects of particulate matter were strengthened when adjusted for NO_2 and SO_2. The ORs with 95% CIs of PM_{10} were 1.119 (95% CI 1.084–1.155) adjusted for NO_2 and 1.153 (95% CI 1.110–1.197) adjusted for SO_2 during the entire pregnancy. Similar to PM_{10}, the ORs with 95% CI of $PM_{2.5}$ were 1.171 (95% CI 1.120–1.223) adjusted for NO_2 and 1.221 (95% CI 1.158–1.288) adjusted for SO_2. However, the effects of NO_2 and SO_2 were not stable, as some of their effects were strengthened, while some were attenuated due to the collinearity between pollutants. The seasonal analysis showed statistically significant associations between air pollution and SGA in summer and winter (Table S3).

Table 3 Estimated ORs with 95% CIs of the risk of SGA for each IQR of air pollutants during each pregnancy period compared with the reference group (lowest quartile)

Pollutant	IQR[a]	Entire pregnancy		Trimester 1		Trimester 2		Trimester 3	
		OR[b] (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
PM_{10}	Q1	–		–		–		–	
	Q2	3.210 (2.124–4.852)	< 0.001	0.858 (0.639–1.152)	0.308	1.012 (0.710–1.443)	0.946	1.375 (0.736–2.019)	0.104
	Q3	3.241 (2.144–4.899)	< 0.001	0.521 (0.373–0.727)	< 0.001	1.224 (0.873–1.716)	0.242	1.942 (1.353–2.786)	< 0.001
	Q4	3.038 (2.004–4.604)	< 0.001	0.475 (0.338–0.667)	< 0.001	1.590 (1.148–2.202)	0.005	2.461 (1.732–3.498)	< 0.001
$PM_{2.5}$	Q1	–		–		–		–	
	Q2	3.167 (2.094–4.789)	< 0.001	0.853 (0.635–1.147)	0.293	1.240 (0.868–1.773)	0.237	1.563 (1.078–2.266)	0.018
	Q3	3.159 (2.088–4.780)	< 0.001	0.570 (0.410–0.793)	0.001	1.398 (0.987–1.980)	0.059	1.665 (1.154–2.401)	0.006
	Q4	3.151 (2.083–4.768)	< 0.001	0.475 (0.337_0.670)	< 0.001	1.772 (1.267–2.478)	0.001	2.385 (1.681–3.384)	< 0.001
NO_2	Q1	–		–		–		–	
	Q2	0.678 (0.483–0.951)	0.024	0.789 (0.587–1.061)	0.116	0.666 (0.464–0.955)	0.027	1.993 (1.369–2.903)	< 0.001
	Q3	0.786 (0.569–1.085)	0.143	0.452 (0.321–0.637)	< 0.001	0.855 (0.612–1.194)	0.358	2.052 (1.412–2.981)	< 0.001
	Q4	0.936 (0.686–1.277)	0.678	0.504 (0.363–0.700)	< 0.001	1.454 (1.072–1.972)	0.016	2.375 (1.646–3.426)	< 0.001
SO_2	Q1	–		–		–		–	
	Q2	0.997 (0.711–1.397)	0.984	0.889 (0.669–1.181)	0.418	1.277 (0.917–1.779)	0.148	1.587 (1.046–2.410)	0.030
	Q3	1.046 (0.752–1.455)	0.790	0.417 (0.297–0.586)	< 0.001	1.022 (0.723–1.445)	0.902	3.138 (2.140–4.063)	< 0.001
	Q4	1.135 (0.822–1.568)	0.442	0.339 (0.235–0.490)	< 0.001	1.309 (0.942–1.819)	0.109	3.074 (2.093–4.515)	< 0.001

[a] Q1: The first quartile; Q2: The second quartile; Q3: The third quartile; Q4: The fourth quartile

[b] Adjusted for maternal age, parity, gestational hypertension, gestational diabetes mellitus, delivery mode, and infant sex

Discussion

This was a cross-sectional study conducted in Huangshi in the eastern Hubei province. Delivery data was collected from the Huangshi Maternity and Children's Health Hospital for the entire year of 2017. In this study, the incidence of SGA was 6.7%, which was lower than the percentile used to define this category (Wang et al. 2019). In this research, exposure to PM_{10} and $PM_{2.5}$ was adversely associated with the risk of SGA during all pregnancy periods. The effects of NO_2 and

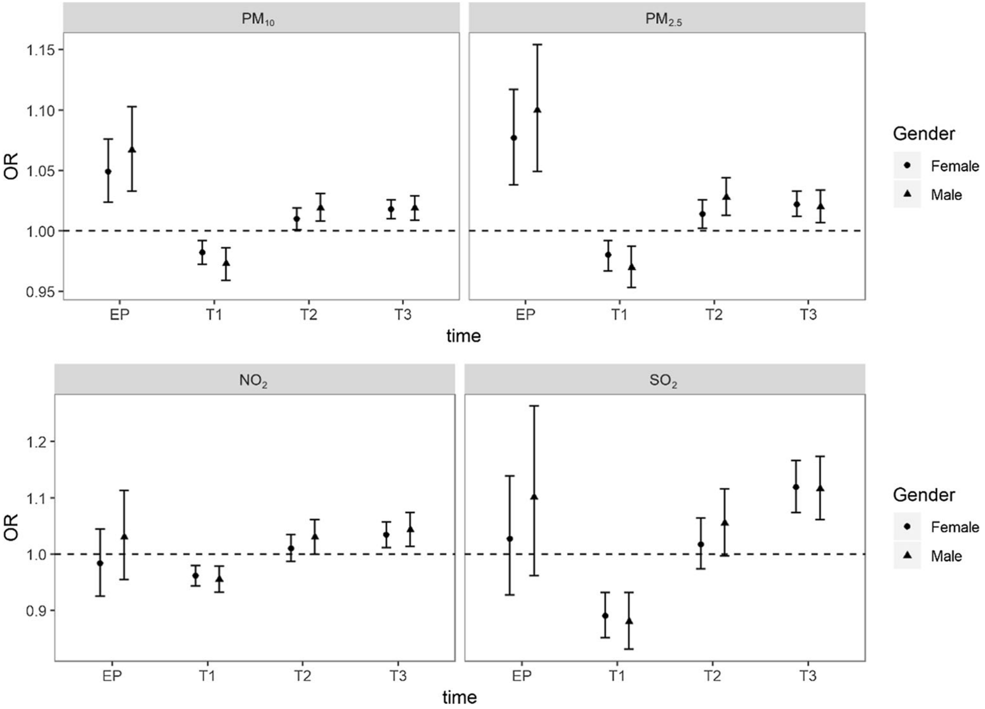

Fig. 3 The estimated ORs of each air pollutant with 95% CIs during different pregnancy periods stratified by sex adjusted for maternal age, parity, gestational hypertension, gestational diabetes mellitus, delivery mode, and infant sex. EP: entire pregnancy, T1: the first trimester, T2: the second trimester, and T3: the third trimester

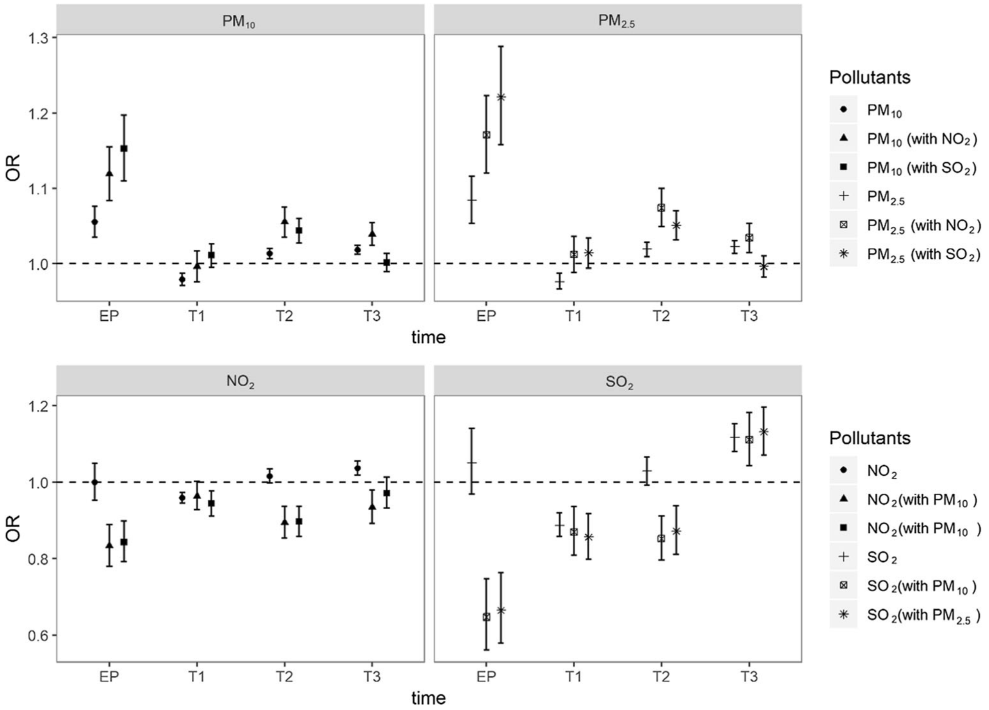

Fig. 4 The estimated ORs for the risk of SGA with 95% CIs in single-pollutant models and multi-pollutant models adjusted for maternal age, parity, gestational hypertension, gestational diabetes mellitus, delivery mode, and infant sex. EP: entire pregnancy, T1: the first trimester, T2: the second trimester, T3: the third trimester

SO_2 exposure were less remarkable, but still significant during the first and third trimesters. This is the first population-based cross-sectional study that has investigated the association between SGA and air pollution in central China. The population selected in this study accounted for more than one-third of the infants delivered in Huangshi in the entire year. Therefore, the population was comparatively representative. Compared with other big cities, Huangshi is a prefecture-level city with a lower residential moving rate, indicating that all of the participants had consistent maternal exposure to pollutants.

With the exception of the first trimester, an increased risk of SGA associated with higher levels of PM_{10} and $PM_{2.5}$ exposure was observed during the other two trimesters. Despite that many previous studies have examined the effects of PM_{10} on SGA, the results have remained inconclusive. While studies have provided multiple evidences for an increased risk of SGA with exposure to PM_{10} in specific trimesters (Ha et al. 2017; Hansen et al. 2007; Le et al. 2012; Mannes et al. 2005), some studies have found a null association between SGA and PM_{10} (Brauer et al. 2008; Capobussi et al. 2016; Kimberly et al. 2014; Madsen et al. 2010; Wang et al. 2019). Unlike PM_{10}, many previous studies have indicated the adverse effects of $PM_{2.5}$ on SGA, as found in this study (Mannes et al. 2005; Percy et al. 2019; Ritz et al. 2007; Stieb et al. 2016), but these studies did not reach a consensus on trimester-specific effects. Identified exposure windows for $PM_{2.5}$ exposure and SGA have been reported in the first trimester (Rich et al. 2009b), the second trimester (Mannes et al. 2005; Wang et al. 2019), the third trimester (Percy et al. 2019; Rich et al. 2009b), and the entire pregnancy period (Stieb et al. 2016).

In addition to the significant relationships during the first trimester, a positive association was found between NO_2, SO_2, and SGA during the third trimester. Some studies have found a positive association between NO_2 exposure and SGA in specific trimesters (Ballester et al. 2010; Stieb et al. 2016; Wang et al. 2019); however, some studies have also reported no evidence of adverse impacts from NO_2 on SGA (Mannes et al. 2005; Rich et al. 2009a; Ritz et al. 2007; Taylor et al. 2016). Previous studies regarding the association between SO_2 and SGA have remained inconclusive, with several studies having reported no association, while others have found a weak association (Ha et al. 2017; Le et al. 2012; Rich et al. 2009a). In summary, previous studies have not observed a stable and positive association between NO_2, SO_2, and SGA.

The discrepancies among this study and previous studies may be attributed to many factors. First, as mentioned, most studies regarding the association between air pollution and SGA have been conducted in developed areas, and the lifestyles of the study populations, such as nutrition, cooking methods, and medical care, which could vary from those of women in Huangshi. Second, many studies adopted more accurate methods based on residential address to estimate the individual exposure, while this study used the mean concentrations collected from monitory station, suggesting a variability of exposure assessment (Percy et al. 2019; Wang et al. 2019). Third, spatial heterogeneity could result in distinct composition of air pollutants, which means that even pollutants with the same concentrations could result in very different exposures (Bell et al. 2010).

In this study, it was found that exposure to ambient air pollution decreased the risk of SGA during the first trimester, which seems not biologically plausible and inconsistent with previous studies. Most studies have found adverse effects from ambient air pollutants. One potential explanation for this discrepancy is that embryos that were easily injured were aborted or resulted in stillbirths in the early maternal stage of air pollutant exposure. However, in this study, only singleton live births were considered; thus, the population that was selected in this study was partially biased (Percy et al. 2019).

During the third trimester, the risk of SGA grew greater than during other periods as the concentration of air pollutants increased. The third trimester is a very important period for fetal growth because the most rapid fetal development occurs in this period (Grantz et al. 2018). Hence, the fetus may be more vulnerable than during other periods. The biological mechanism of the adverse impacts from air pollution on newborns remains unclear. It is assumed that air pollutants could alter fetal growth by causing oxidative stress or inflammation, reducing placental exchange of nutrients and gases, negatively affecting placental growth, fostering endocrine disruption, or causing negative maternal health effects (Kannan et al. 2006). Another hypothesis is that air pollution can affect the mitochondria. For instance, exposure to NO_2 causes damage to mitochondrial DNA, which is related to infant birth weight (Clemente et al. 2016). Prenatal PM_{10} exposure has been associated with placental mitochondrial alterations, which may both reflect and intensify oxidative stress production (Janssen et al. 2012).

In this time-stratified analysis, it was found that exposure to air pollution in summer and winter was associated with SGA morbidity. The increased risk of SGA in summer may be the result of high-temperature exposure. Heat stress could cause damage to the antioxidant defense system and result in a larger secretion amount of oxytocin (Forgati et al. 2017), which could have a negative impact on maternal health and fetal growth. The association in winter could be explained by a deficiency in vitamin D. Vitamin D has been found to be negatively correlated to SGA risk (Wang et al. 2018), and the level of vitamin D in winter in China is much lower than that in summer (Yang and Zhang 2013).

In the subgroup analysis, it was found that the effects of environmental exposure to air pollution could be modified by infant sex, which has been mentioned in many previous studies (Lee et al. 2014; Liu et al. 2018; Taylor et al. 2016; Wainstock et al. 2014). Lee et al. (2014) suggested that prenatal exposure to bisphenol A played a different role in birth weights between male infants and female infants in a multicenter birth cohort study from Korea (Lee et al. 2014). A study in Shanghai, China, found that maternal exposure to household air pollution could contribute to adverse birth outcomes in boys but not in girls (Liu et al. 2018). However, a population-based study in the UK showed that moderate prenatal cadmium exposure was associated with lower birth weights in girls but not in boys (Taylor et al. 2016). In addition, one retrospective cohort study reported that exposure to prenatal maternal stress was a risk factor only in female fetuses (Wainstock et al. 2014). These findings suggest that sexual differences may alter the effects of the external environment, and variations between sexes should be noticed. Some studies have attempted to provide biologically plausible explanations for these variations. Male fetuses were assumed to have greater potential susceptibility to a pro-inflammatory environment during pregnancy. In vitro studies have shown that when infected, cells from pregnancies with a male fetus were observed to have an increase in production of pro-inflammatory cytokines, including tumor necrosis factor and prostaglandin synthase, and had a smaller quantity of anti-inflammatory cytokines and prostaglandin dehydrogenase compared with female infants (Al-Qaraghouli and Fang 2017; Challis et al. 2013; Liu et al. 2018).

The quartile assessment showed that the risk of SGA under exposure to PM_{10} and $PM_{2.5}$ was not distinct during the entire pregnancy. However, the trimester-specific analysis showed that the effects of PM_{10} and $PM_{2.5}$ became stronger with increasing concentrations, suggesting that the risk for SGA could increase without a threshold effect of pollutants as the concentration of PM_{10} and $PM_{2.5}$ increased. The associations between NO_2, SO_2, and SGA were not as stable as particulate matter, but an OR increase in SGA still was observed per IQR increase during the third trimester. Previous studies have not reached a consistent conclusion on how air pollutants with different quartiles affect SGA, as they have reported no significantly positive associations or even a decreased risk of SGA for higher levels of PM_{10} and NO_2 (Eh et al. 2012; Hansen et al. 2007; Wu et al. 2018). In summary, whether higher concentrations of air pollutants will lead to increased risk of SGA requires further research.

Several limitations should be considered when interpreting this research. The accurate address of each pregnant woman was not acquired. Therefore, the mean concentration of each air quality monitoring station in Huangshi was used to replace individual exposure. The lack of an accurate maternal exposure model may lead to some misclassifications due to the fact that air pollutant concentration levels are not homogenous across different locations. In this cross-sectional study, only pregnancy data for the year of 2017 was collected, which is a research period restriction. In further studies, a larger cohort that covers several continuous years needs to be collected to observe the effect of air pollution on SGA based on a retrospective study. Due to the hospital location in central Huangshi, the population recruited was primarily from the urban city; thus, the condition of rural areas could not be presented in this research.

In this study, although SGA was found to have a 2% to 10% increased risk when exposed to air pollution during the third trimester, considering the high concentration of air pollutants in Huangshi, exposure to ambient air pollution is still a severe risk factor for fetal growth restriction. Therefore, these findings are significant enough to encourage the government to take actions to reduce air pollutant emissions to improve the health condition of pregnant women and their infants. It is worthwhile to continue air quality improvements for the prevention of SGA infants and to reduce the costs associated with SGA infants later in life.

Conclusion

In this cross-sectional study, it was found that maternal exposure to air pollution was significantly associated with SGA. Overall, the adverse effects of PM_{10} and $PM_{2.5}$ were stronger than gaseous pollutants, including NO_2 and SO_2. In addition, the third trimester was found to be the most vulnerable period for fetuses when exposed to air pollution. These findings can provide a basis for air quality management policies and the promotion of neonatal health. More studies in other prefecture cities with high levels of air pollutants should be conducted, which conform to this study in the future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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